Journal of Geriatric Oncology 12 (2021) 1044–1051

Contents lists available at ScienceDirect

Journal of Geriatric Oncology

The impact of timely cancer diagnosis on age disparities in colon cancer survival

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ARTICLE INFO

Article history:
Received 14 December 2020
Received in revised form 1 March 2021
Accepted 7 April 2021
Available online 15 April 2021

Keywords:
Colon
Cancer
Survival
Older adults
Aged
Population-based cancer registry
Observational data

ABSTRACT

Objective: We described the role of patient-related and clinical factors on age disparities in colon cancer survival among patients aged 50–99 using New Zealand population-based cancer registry data linked to hospitalisation data.
Method: We included 21,270 new colon cancer cases diagnosed between 1 January 2006 and 31 July 2017, followed up to end 2019. We modelled the effect of age at diagnosis, sex, ethnicity, deprivation, comorbidity, and emergency presentation on colon cancer survival by stage at diagnosis using flexible excess hazard regression models.
Results: The excess mortality in older patients was minimal for localised cancers, maximal during the first six months for regional cancers, the first eighteen months for distant cancers, and over the three years for missing stages. The age pattern of the excess mortality hazard varied according to sex for distant cancers, emergency presentation for regional and distant cancers, and comorbidity for cancer with missing stages. Ethnicity and deprivation did not influence age disparities in colon cancer survival.
Conclusion: Factors reflecting timeliness of cancer diagnosis most affected age-related disparities in colon cancer survival, probably by impacting treatment strategy. Because of the high risk of poor outcomes related to treatment in older patients, efforts made to improve earlier diagnosis in older patients are likely to help reduce age disparities in colon cancer survival in New Zealand.

1. Introduction

Older patients with colon cancer have poorer cancer survival than younger patients [1]. The disadvantage in cancer survival in older adults has even been widening [1], suggesting that they have not benefitted from the improvements in cancer diagnosis and treatment at the same magnitude as younger people. Previous work showed that low survival in older patients with colon cancer was mainly explained by a high excess hazard in the first year after diagnosis [2].

Because of age-related physiological changes, comorbidity, and polypharmacy, older patients have a higher risk of drug interaction, and chemotherapy-related toxicity [3]. They are also more likely to have comorbidities [4], cognitive impairment [5], to be depressed [6], and isolated with poor social support [7]. In addition, older patients are seldom included in randomized clinical trials [8]. Physicians have, therefore, to extrapolate from evidence based on younger patients to adapt new treatment strategies to older patients. As a consequence, older patients with cancer are likely to receive suboptimal treatment [9]. Besides, they are more likely to be diagnosed with cancer after an emergency presentation, and this has been associated with poor cancer survival [10].

The magnitude of the age disparity in colon cancer survival varied inconsistently by stage at diagnosis, sex, ethnicity, and socioeconomic factors across studies [11]. While age is an important prognostic factor, only a few population-based studies described the role of patient and clinical factors on age disparities in colon cancer survival per se[11].

In New Zealand, colon cancer was the second most common cancer and the second biggest cause of cancer deaths in adults aged 70 years or older in 2018 [12]. The most recent five-year net survival estimates for colon cancer was 62% (95% confidence interval: 61%–63%), similar to most western countries [1]. New Zealand has universal healthcare coverage, with some co-payments for primary care but no cost at point of

Abbreviations: EMH, excess mortality hazard; ICD, International Classification of Disease; SEER, Surveillance, Epidemiology and End Results.

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https://doi.org/10.1016/j.jgo.2021.04.003

delivery for secondary/ hospital care. There is also some private provision of surgical and oncology care.

Using New Zealand population-based cancer registry data linked to hospitalisation data, we describe, for the first time, the contribution of sex, ethnicity, deprivation, comorbidities, and emergency presentation on age disparities in colon cancer survival.

2. Methods

The full description of method including the statistical analysis is in Supplementary Methods. We included new colon cancer cases (ICD-10 codes C18.0-C18.9) diagnosed between 1 January 2006 and 31 July 2017 from the New Zealand population-based cancer registry, that we linked to hospitalisation data for the five years before the cancer diagnosis, and to the outpatient dataset where all emergency admissions are recorded. Rectal cancer cases (ICD10: C20), and all rectosigmoid cancer cases (ICD10: C19) were excluded. We obtained the date of death for all cancer cases dead by 31 December 2019 from the Ministry of Health. We restricted our analyses to patients aged between 50 and 99 years old at diagnosis with a first occurrence of colon cancer.

We categorised the extent of disease as given by the cancer registry into Surveillance, Epidemiology and End Results (SEER) stage groups as follows: Localised to the organ of origin or invasion of adjacent tissue or organ into SEER localised stage; Regional lymph nodes involvement into SEER regional stage; Distant into SEER distant stage; Not known into missing stage [13].

We used the "all-sites" weighted C3 index that has been developed from 42 conditions and validated using New Zealand cancer data to assess comorbidity among patients with cancer using administrative hospitalisation data [14]. In brief, a weight is assigned to each comorbid condition. The weight corresponds to the parameter estimate (i.e., the log hazard ratios) in the Cox regression model of noncancer death, adjusting for age, site and stage. The index scores were calculated for each patient by adding together all parameter estimates for all comorbid conditions recorded for that patient [14]. We defined emergency presentation at diagnosis as a cancer diagnosis occurring in the 28 days following admission to an emergency department [15].

Sex and age at diagnosis were available for all cases within the cancer registry. We assessed the socio-economic deprivation at cancer diagnosis using the New Zealand Deprivation Index [16]. We could not map domicile code to deprivation index for 36 patients, who were, therefore, excluded from analyses.

Self-reported ethnicity, available in the cancer registry, originated from the health records. We grouped patients into Māori and non-Māori. The ethnicity was not available for 249 patients, who, were, therefore, excluded from analyses.

2.1. Statistical Analysis

For each stage at diagnosis, we derived net survival from the estimation of individual excess mortality hazard (EMH) using flexible excess hazard regression models. We created lifetables of mortality in the general population from those obtained from Statistic New Zealand. We censored all patients who were still alive beyond five years after diagnosis for model stability at the tails [17]. For each stage, we first defined the functional form of the baseline hazard. Then, we selected the final model using the strategy of Wynant and Abrahamowicz adapted for relative survival setting by Maringe et al. [18] We forced the lifetable variables (i.e. sex, age, ethnicity, year at diagnosis) into the models. We tested the non-linear effect of age at diagnosis, year of diagnosis and comorbidity score. For all covariates, we tested for time-dependent effects and their interaction with age at diagnosis using the Likelihood Ratio Test.

We performed data management using Stata (version 16.0; StataCorp, 2019) and statistical analyses using R statistical software (version 3.4.0; R Development Core Team, 2017), in particular the 'mexhaz' package was used for flexible excess hazard modelling [19].

2.1.1. Ethics Approval

The University of Otago Human Ethics Committee (Health) approved the study (Ethics Committee reference number HD19/048).

3. Results

Out of 2, 003 patients diagnosed with colon cancer between January 2006 and July 2017, we included 21,270 patients aged 50–99 (median age at diagnosis = 74, interquartile range 67–81; 51.7% females). Table 1 presents the characteristics of the included patients by age at diagnosis, and Supplementary Table 1 by age at diagnosis and stage at diagnosis. While patients under 75 years old were mostly males, older patients were mainly females. Non-Māori constituted the majority of the newly diagnosed patients, and their percentage increased as the age at diagnosis increased. Deprivation level was evenly distributed across age groups. Overall, 24.0% of patients were diagnosed with localised cancer, 43.2% with regional cancer, 21.3% with distant cancer, and 11.4% had a missing stage. The percentage of missing stage increased after the age of 75, and it was twice higher in the 85–99 age group than in the 75–84 age group. The comorbidity score increased with age, with over three quarters of patients aged over 85 who had a positive comorbidity score compared to half of patients aged 50–64. Overall, 29.7% of patients were diagnosed with colon cancer after an emergency presentation, and the percentage was the highest in the oldest age group.

The one-, and three- year net survival estimates were, respectively, 98.1% (95% confidence interval: 97.6%–98.5%), and 95.8% (95.0%–96.6%) in patients with localised stage, 91.4% (90.7%–92.0%), and 79.8% (78.8%–80.8%) in patients with regional stage, 38.3% (37.0%–39.6%), and 15.9% (14.9%–17.0%) in patients with distant stage, and 55.2% (53.3%–57.1%), and 35.1% (33.1%–37.0%) in patients with missing stage. Net survival decreased as the age at diagnosis increased in all stages, but the disadvantage in older patients was more evident in advanced cancers and for cancer with missing stage (Fig. 1, Supplementary Table 2).

One-year net survival did not differ much by sex for localised stage (Fig. 2). For regional stage, one-year net survival was similar across sexes up to 80 years old, then females had better net survival than males. For distant stage, net survival in females decreased almost

Table 1
Patients' characteristics by age group.

Age categories (years)	50–64	65–74	75–84	85–99
Cases (%)	4212 (19.8)	6614 (31.1)	7371 (34.7)	3073 (14.4)
Male (%)	2193 (52.1)	3499 (52.9)	3458 (46.9)	1126 (36.6)
Ethnicity (%)				
Māori	384 (9.1)	335 (5.1)	208 (2.8)	43 (1.4)
Non-Māori	3828 (90.9)	6279 (94.9)	7163 (97.2)	3030 (98.6)
Deprivation Index quintiles (%)				
1 - Less deprived	831 (19.7)	1182 (17.9)	1133 (15.4)	463 (15.1)
2	782 (18.6)	1244 (18.8)	1353 (18.4)	553 (18.0)
3	873 (20.7)	1450 (21.9)	1673 (22.7)	700 (22.8)
4	946 (22.5)	1587 (24.0)	1882 (25.5)	816 (26.6)
5 - Most deprived	780 (18.5)	1151 (17.4)	1330 (18.0)	541 (17.6)
Stage at diagnosis (%)				
Localised	1020 (24.2)	1712 (25.9)	1854 (25.2)	529 (17.2)
Regional	1782 (42.3)	3060 (46.3)	3261 (44.2)	1087 (35.4)
Distant	1115 (26.5)	1392 (21.0)	1405 (19.1)	619 (20.1)
Missing	295 (7.0)	450 (6.8)	851 (11.5)	838 (27.3)
Comorbidity score > 0 (%)	2159 (51.3)	4123 (62.3)	5394 (73.2)	2408 (78.4)
Comorbidity score (median [IQR])	0.39 [0.00,1.27]	0.75 [0.00,1.89]	1.21 [0.00,2.71]	1.38 [0.52,2.81]
Emergency presentation (%)	1225 (29.1)	1746 (26.4)	2164 (29.4)	1176 (38.3)

IQR: Inter-quartile range.

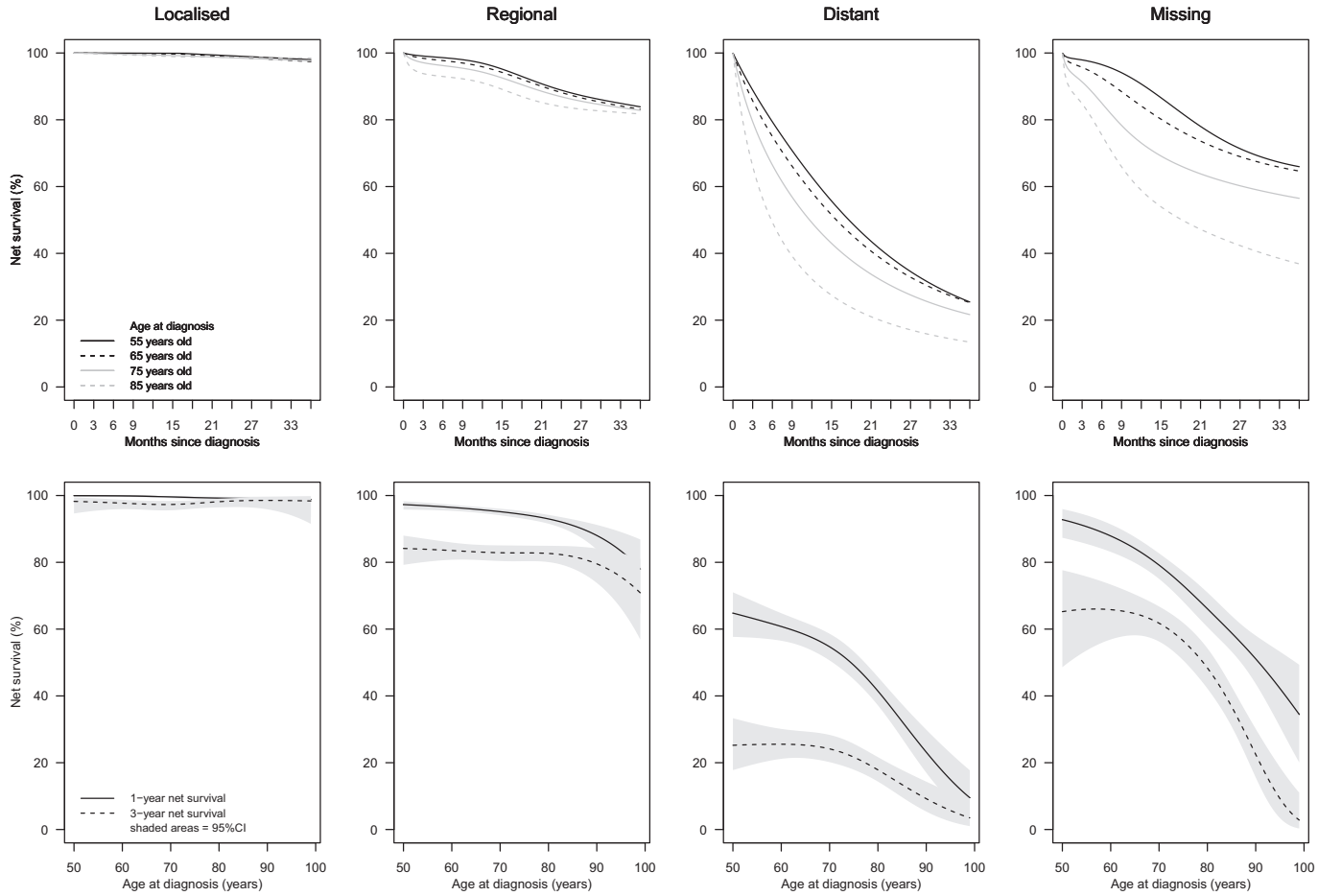

Fig. 1. Net survival for patients aged 55, 65, 75 and 85 years old over the first three years after diagnosis by stage at diagnosis (top panel) and one-and three-year net survival by age at diagnosis and stage at diagnosis (bottom panel).

linearly as age increased, while it is not the case for males. Males aged 65–85 years old had better survival than females. Females with missing stage had lower net survival than males. Māori with localised stage had similar net survival than non-Māori regardless of the age at diagnosis. For the other stages, Māori had poorer net survival than Non-Māori. For regional and distant stages, net survival decreased as the deprivation index increased, but the difference across deprivation index quintiles was small, and similar over time. Net survival decreased as comorbidity score increased for localised and regional cancers. However, patients with higher comorbidity level had better survival than those with lower level for distant cancer. For missing stage, patients with high comorbidity level had poorer survival than other patients up to 70 years old. Afterwards, they had better net survival. Patients diagnosed with colon cancer after an emergency admission had poorer net survival regardless of the stage or the age at diagnosis. The difference in one-year net survival between those who had an emergency presentation and those who had not increased as age increased, except for distant cancers for whom the reverse was observed. Similar results are observed three years after diagnosis (Supplementary Fig. 1), with a few exceptions. Māori with distant stage had slightly better three-year net survival than non-Māori. Difference in net survival across comorbidity levels were more marked for localised and regional cancers at three than at one year since diagnosis. Patients with higher comorbidity level had poorer three-year net survival than others when cancer was diagnosed at later stage. For missing stage, patients with higher comorbidity level had significantly poorer net survival than other but differences disappeared after the age of 80.

To better understand the age difference in net survival, we looked at the age pattern of excess mortality hazard over time (Fig. 3). For localised stage, the EMH was low for all ages, with a slight disadvantage for older patients during the first fifteen months after diagnosis. The tendency was reversed afterwards. For regional stage, the excess mortality in older patients was obvious during the first six months after diagnosis. Then, the EMH ratios were close to 1 for all ages. For distant stage, older patients had higher excess mortality than younger patients for eighteen months after diagnosis. Then, the curves converged for all ages, and the EMH ratios were close to 1. For missing stage, the excess in mortality in older patients was highest during the first year after diagnosis and persisted over entire follow-up for the oldest patients.

We tested the modification effect of factors on the relationship of age at diagnosis with the EMH (Supplementary Table 3). For localised stage, no factors modified the age pattern of the EMH. For regional stage, the effect of age on the EMH was greater in patients diagnosed after an emergency presentation than other patients, especially in the first three months after diagnosis (Fig. 4A). For distant stage, patients who were not diagnosed after an emergency presentation had higher EMH ratios than those who had an emergency presentation, mainly in the first six months (Fig. 4B). The EMH ratio reached 1 after the first year for patients with an emergency presentation, and later for the other patients. Females had higher EMH ratios compared to males over the entire follow-up time. However, the sex difference was greatest in the first three months after diagnosis and decreased afterwards to become negligible at three years (Fig. 4C). For missing stage, comorbidity level modified considerably the effect of age on the EMH, with EMH ratios of up to 10 for patients with 25th percentile comorbidity score. The lower comorbidity score, the higher the EMH ratio, mainly in the first six months after diagnosis and in patients older than 80 years old (Fig. 4D).

4. Discussion

This study, for the first time, provides a comprehensive description of patient-related and clinical factors that influence the effect of age at diagnosis on the excess mortality hazard in patients with colon cancer aged over 50 in New Zealand. The stage at diagnosis and an emergency presentation at diagnosis modified the most the age disparity in colon cancer survival, while comorbidity played little role. About patient-related factors, sex was the sole factor that influenced age disparities in cancer survival but only in patients with

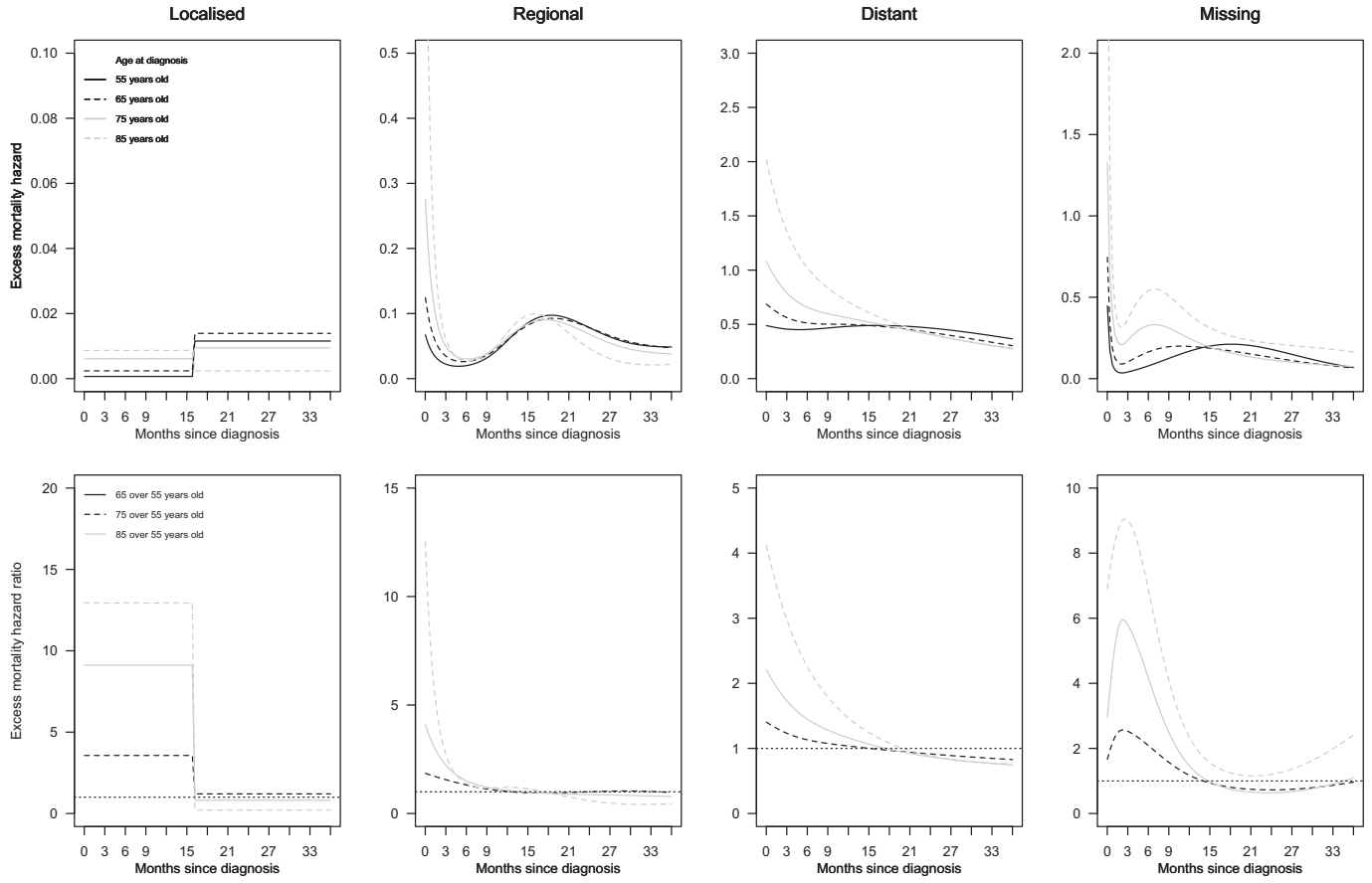

Fig. 3. Excess mortality hazard for patients aged 55, 65, 75 and 85 years old (top panel), and excess mortality hazard ratio for patients aged 65, 75 and 85 years compared to patients aged 55 years old during the first three years since diagnosis by stage at diagnosis (bottom panel).

distant cancer, females having greater age difference in net survival than males.

The female advantage in colon cancer survival in patients aged under 65 years old is congruent with findings from the EUROCARE study [20]. In Finland, the absolute difference in one-year relative survival between the 45–59-year group and the 75-and-over group was also higher in females compared to males with distant colon cancer [21]. As suggested by others, the interaction between the age at diagnosis and sex indicates possible involvement of sex hormones [20]. However, the causal mechanism explaining this interaction and the reason why this concerns only patients with distant cancer remain unclear and deserve further investigation.

We are not aware of other studies looking at the effect of ethnicity on age disparities in colon cancer survival. One United States study showed black patients with colorectal cancer had greater age disparity in five-year net survival than white patients, mainly explained by poorer survival among black patients aged over 75 compared to white patients [22]. Because the relationship between ethnicity and healthcare system is complex and specific to each country's history, any comparisons across countries are not relevant. While our study confirmed the negative effect of deprivation on colon cancer survival [23], we did not find any evidence of its role in age disparities in colon cancer survival.

Comorbidity is highly prevalent in patients with colon cancer, especially in older patients, and may affect the likelihood to receive treatment, and impact survival [24]. However, our results suggest that comorbidity does not fully explain the age disparity in colon cancer survival. Indeed, for cancers with known stage, the effect of age on the excess hazard of death was the same across all comorbidity levels, suggesting that comorbidity affects cancer management regardless of the age at diagnosis. All aspects of comorbidity may not be well captured with hospitalisation data, especially when comorbidity did not require hospitalisation. However, in New Zealand, the C3 index performed slightly better than a comorbidity index based on pharmaceutical data, that identify patients who had drug prescription for diseases irrespective of whether the patient was hospitalised or not [25]. A difference in treatment based on the chronological age or the existence of other unmeasured factors may explain lower survival in older patients without comorbidity. Indeed, comorbidity alone does not reflect the overall fitness status of patients. As older patients are heterogeneous in terms of health status and fitness, the comprehensive assessment of common geriatric conditions including functional status, falls, cognition, nutritional status, social support helps identifying patients who may benefit the most from cancer treatment [26]. However, to date, such information is not currently available at population level.

Factors related to timeliness of cancer diagnosis — i.e., the stage at diagnosis and an emergency presentation — greatly affected age disparities in colon cancer survival, reflecting the effect of cancer management on survival. The treatment phase is a critical period where age inequalities occur [27], likely because physicians are lacking evidence-based treatment strategies, especially in comorbid and oldest patients [8]. Surgery is the standard treatment in early-stage colon cancers, but older patients have a reduced likelihood of undergoing surgery [28]. They also experienced higher post-operative mortality rates [29]. In New Zealand, the percentage of death within 90 days of resection was 7.3% in patients aged over 75, and 4.8% after elective resection against 1.5–2.9% and 0.0–1.7%, respectively, in younger patients [29]. In New Zealand, patients over 75 years old were nine-times less likely to receive chemotherapy than those aged 25–54 years old [30]. Yet, evidence suggests that fit older patients may benefit from the same regimen of chemotherapy as middle-aged patients [31], and less intensive therapies may be used in

unfit older patients [32]. The current New Zealand guidelines for non-metastatic colon cancer management do not include recommendations regarding chemotherapy or surgery tailored to older patients [33]. Yet, without appropriate stratification, older patients are more likely to receive suboptimal treatment compared to middle-aged patients. Further observational studies to investigate how treatment may influence age disparities in colon cancer survival at population-level are needed. However, these studies should be properly designed to remove the risk of immortal-time bias, arising when the time of treatment initiation does not coincide with time of cancer diagnosis [34].

Consistently with previous studies [10], we showed that older adults were more prone to be diagnosed through emergency settings than

middle-aged patients. A diagnosis following an emergency presentation was associated with a lower chance of curative treatment and an excess risk of mortality, particularly in the initial months after diagnosis [10]. This is consistent with many other studies which have demonstrated consistently poorer outcomes in people diagnosed as an emergency, as well as older people being more likely to present urgently [10]. Emergency surgery is challenging but outcomes have been shown to be better in the hands of specialist, rather than generalist, surgeons [35] and in older patients full geriatric assessment and multidisciplinary management improves care [36]. Given screening programmes often only include people up to the age of 75 their ability to reduce emergency presentation rates in the oldest populations is limited and so focussing on optimising care for such cases is important if outcomes are to be improved in older adults.

Because of the high risk of poor outcomes related to treatment in older patients, effort should be made on reducing delays in colon cancer diagnosis. The roll-out of the national colorectal cancer screening program began in 2017. Evidence suggests that colorectal cancer screening program decreased the risk of an emergency admission to hospital prior to a colorectal cancer diagnosis in adults targeted by screening program [37], however, this positive effect may not be observed in older adults. Besides, colon cancer symptoms, including abdominal pain, diarrhoea, and constipation, have low specificity [38] and are prevalent in older patients, especially in individuals with other comorbid conditions. While there was no publicly funded campaign of awareness of colon cancer symptoms during the study period, the colorectal cancer screening program launched in 2017 undoubtedly increase awareness of colorectal cancer. At the patient level, presence of comorbidity increased the likelihood to be diagnosed with distant colorectal cancer in New Zealand [39]. However, tumour stage was not correlated with the delay from the onset of symptoms to the administration of definite treatment [40]. Still, the potential effect of age was not analysed, and the audit was restricted to one hospital only [40]. It is also possible that older people are more likely to face barriers to timely accessing health care because of socio-economic factors [41]. A comprehensive understanding of factors influencing timely diagnosis of colon cancer in older adults is warranted in New Zealand to develop interventions to improve earlier cancer diagnosis, regardless of age, that will ultimately reduce age disparities observed at the population level.

Our study has limitations. The estimation of net survival relies on the background mortality rates obtained from lifetables, and implies that one matches patients with cancer to individuals from the general population that should ideally present the same characteristics (sex, age, socio-economic level, etc.) as patients except for cancer. When one is interested in the effect of age on cancer survival, characteristics, such as comorbidity, that influences both background mortality and cancer mortality, have their importance, but are unavailable at population level. Consequently, the estimation of excess mortality hazards may be overestimated, and therefore our net survival estimates underestimated [42]. Additionally, we acknowledge that age disparities in colon cancer survival may differ depending on other unstudied factors such as those related to the tumour (e.g. histology or the number of positive lymph nodes involved) [11], or to access to health care system, or more importantly, those influencing the receipt of treatment (e.g. frailty, functional status, nutritional status, specific comorbidity, etc.). However, in the present study, we restricted the number of variables investigated because of the relatively low number of cases by stage. Another essential aspect is patients' preference about treatment, particularly important to consider as they age. Unfortunately, this aspect is difficult, even impossible, to capture using observational data. Another limitation relies on the lack of validation of the definition we use for an emergency presentation at diagnosis in the New Zealand setting. However, the definition being based on the existence of hospital records only, and not on clinical coding, the Elliss-Brooke et al. definition should perform well. This should be, however, investigated in future studies. Finally, studied factors may have different effects on age disparities in cancer survival in other high-income countries because of differences in the health-care system. Similar studies in other countries would be interesting to test the generalizability of our findings.

5. Conclusion

The present population-based study shows that factors reflecting timeliness of cancer diagnosis affected the most the age difference in colon cancer survival, probably due to their impact on treatment strategy. In contrast, comorbidity and patient-related factors play a negligible role. It is Utopian to believe that colon cancer survival in older patients may equal that in middle-aged patients. However, there are opportunities for enhancement, notably in improving earlier diagnosis in older adults. Efforts towards this goal are likely to help reduce age disparities in colon cancer survival in New Zealand.

Data Accessibility

The data that support the findings of this study are available from New Zealand Ministry of Health (Data-enquiries@health.govt.nz). Restrictions may apply to the availability of these data outside New Zealand. See https://www.health.govt.nz/nz-health-statistics/access-and-use/data-request-form.

Funding

This work was supported by the European Union's Horizon 2020 Research and Innovation Programme, Belgium under the Marie Skłodowska-Curie grant agreement No 842817 to Sophie Pilleron.

Authors' Contributions

Conceptualization; SP. Data curation; SP, JA. Formal analysis; SP. Funding acquisition; SP. Investigation; N/A. Methodology; SP, CM, HC. Project administration; SP. Resources; N/A. Software; N/A. Supervision; DS, EM. Validation; N/A. Visualization; N/A. Writing - original draft; SP. Writing - review & editing. SP, CM, HC, JA, EM, DS.

Declaration of Competing Interest

The authors declare no conflict of interest.

Acknowledgments

We thank New Zealand cancer registry staff for their fantastic work and their help in understanding cancer data. We also thank Kendra Telfer for her immeasurable help in understanding NZ datasets and Dr. Nicholas West for answering our questions about cancer pathology.

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2021.04.003.

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